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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/092,639	03/07/2002	Walter Schuler	4-100-8303C/C1D1	8447

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NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
WEDDINGTON, KEVIN E	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 03/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

4/C

Office Action Summary	Application No.	Applicant(s)	
	10/092,639	SCHULER ET AL.	
	Examiner	Art Unit	
	Kevin E. Weddington	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/712,359.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 11-28 are presented for examination.

The preliminary amendment filed March 7, 2002 and the information disclosure statements filed October 2, 2002 and January 5, 2004 have been received and entered.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/712,359, filed on November 11, 2000.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating neointimal proliferation and thickening and/or restenosis and/or vascular occlusion following vascular injury or manifestations of chronic rejection in a recipient of organ or tissue transplant or acute or chronic rejection in a recipient or organ or tissue xenograft transplant with the administration of only 40-O-(2-hydroxy)ethyl-rapamycin, does not reasonably provide enablement for preventing neointimal proliferation and thickening and/or restenosis and/or vascular

occlusion following vascular injury or manifestations of chronic rejection in a recipient or organ or tissue xenograft transplant with the administration of 40-O-(2-hydroxy)ethyl-rapamycin and a second agent disclosed in claims 11 and 20. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per factors indicated in the decision In re Wands, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation.

The factors include:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to preventing neointimal proliferation and thickening and/or restenosis and/or vascular occlusion following vascular injury or manifestations of chronic rejection in a recipient or organ or tissue xenograft transplant with the administration of 40-O-(2-hydroxy)ethyl-rapamycin and a second agent disclosed in claims 11 and 20.

The relative skill of those in the art is generally that of a Ph.D. or M.D.

There are no known preventative therapies for neointimal proliferation and thickening and/or restenosis and/or vascular occlusion following vascular injury or manifestations of chronic rejection in a recipient or organ or tissue xenograft transplant.

It is clear the art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy.

The amount of direction or guidance provided and the presence or absence of working examples

The working examples are limited to the administration of 40-O-(2-hydroxy)ethyl-rapamycin only.

There are no examples showing the instant composition comprising 40-O-(2-hydroxy)ethyl-rapamycin and a second agent disclosed in claims 11 and 20 will, in fact, prevent neointimal proliferation and thickening and/or restenosis and/or vascular occlusion following vascular injury or manifestations of chronic rejection in a recipient or organ or tissue xenograft transplant especially in a recipient not presently at risk of or predisposed to developing such a condition.

Current modes of treatment as known, but there are no known agents (alone or in combinations) which can prevent neointimal proliferation and thickening and/or restenosis and/or vascular occlusion following vascular injury or manifestations of chronic rejection in a recipient or organ or tissue xenograft transplant.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to which particular cause would be to prevent neointimal proliferation and thickening and/or restenosis and/or vascular occlusion following vascular injury or manifestations of chronic rejection in a recipient or organ or tissue xenograft transplant with the administration of 40-O-(2-hydroxy)ethyl-rapamycin and a second agent. The skilled artisan would expect that interaction of a particular drug in the prevention of the said condition to be very

specific and highly unpredictable absent a clear understanding of the structural and biochemical basis of the agent. The instant specification set forth no such understanding or any criteria for extrapolating beyond the administration of 40-O-(2-hydroxy)ethyl-rapamycin and a second agent to prevent the instant condition. Even for the data presented, no direction is provided to prevent the said condition and it causes. Absent reasonable *a priori* expectations of success, one skilled in the art would have to test extensively many conditions that may lead to the specific conditions of claims 11 and 20 to discover which cause is prevented. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to practice the invention as its is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

Claims 11-28 are not allowed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the

various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cottens et al. (5,665,772 or AC of PTO-1449) in view of Morris et al. (5,516,781 or AB of PTO-1449).

Cottens et al. teach methods of treating or preventing organ or tissue transplant rejection and preventing graft-versus-host disease, as well as methods of treating inflammatory and proliferative disorders with applicants' claimed rapamycin derivatives, including 40-O-(2-hydroxyl)ethyl-rapamycin. (See columns 1, 2, 3 (lines 24-32, 4 (line 1), Example 8 in column 12 and claims 8 and 9. Also note particularly column 4, lines 56-65 states the claimed rapamycin derivatives, including 40-O-(2-hydroxy)ethyl rapamycin can be administered together with other drugs. Note the other drugs are the same as the applicants' as disclosed in claims 11 and 20, such as, ciclosporin, FK-506, or their immunosuppressive derivatives; corticosteroids; azathioprene; immunosuppressive monoclonal antibodies and other immunomodulatory compounds.

The instant invention differs from the cited reference in that the cited reference does not teach the instant combination is used to prevent or treat restenosis and/or vascular occlusion following vascular injury. However, the secondary reference, Morris et al., teaches rapamycin is effective at preventing and treating intimal thickening of smooth muscle cells in blood vessels, restenosis, and vascular occlusion resulting from vascular injury (See columns 3 and 4 and the claims). Although applicants' claims are directed to 40-O-(2-hydroxy)ethyl-rapamycin than rapamycin itself, one skilled in the art would have assumed the 40-O-(2-hydroxy)ethyl-rapamycin would possess the same activity similar to rapamycin since both prior art references teach that rapamycin and the claimed derivatives thereof possess immunosuppressive, anti-inflammatory, and antiproliferative activity in the absence of evidence to the contrary.

Claims 11-28 are not allowed.

The reference listed on the enclosed PTO-892 is cited to show the state of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin E. Weddington whose telephone number is (571)272-0587. The examiner can normally be reached on 11:00 am-7:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)272-0951. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kevin E. Weddington
Primary Examiner
Art Unit 1614

K. Weddington
March 6, 2005